bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

Please add the following new claim:

--21. The method of claim 1, wherein the compound is non-immunosuppressive.--

REMARKS

The specification has been amended to insert the title of the invention, to correct obvious typographical errors and to describe the inventive subject matter more clearly. Claims 12-20 have been canceled; and claims 1, 2, 3 and 7 have been amended, and new claim 21 has been added to describe the inventive subject matter more clearly. Upon entry of the above amendments, claims 1-11 and 21 are pending in the application.

The amendments do not introduce new matter within the meaning

of 35 U.S.C. § 132. Basis for the amendments to the specification may be found at page 1, lines 7-11 and page 73, last line of the text; in claim 1 as originally filed; and elsewhere throughout the specification and claims. Basis for the amendments to the claims may be found at page 34, line 10; in claims 2, 3 and 7 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Objections to the Content of the Specification

The Office Action objects to the content of the specification for the following reasons:

> "The content of the specification does not conform with to the preferred content of a patent application for prosecution in front of the United States Patent and Trademark Office...."

Applicants respectfully traverse this objection because it provides only general guidelines and fails to state any error or omission to which the objection is directed. To the extent that Applicants have been able to do so without guidance in the Office Action, the foregoing amendments to the specification obviate this objection.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this objection.

2. Rejection of Claims 12-20 under Judicially Created Doctrine of Obviousness-type Double Patenting

The Office Action rejects claims 12-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,786,378. As the basis for this rejection, the Office Action states:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the pharmaceutical compositions of heterocyclic thioesters of Formula I of the instant claims have been set forth as pharmaceutical compositions in the claims cited supra of '378. The claims of the instant application differ only by the addition of further alkyl and aromatic groups, which constitute obvious substitutions in the Markush groups of the analogous compounds set forth in '378.

Contrary to the Office Action, the present application does not claim "heterocyclic thioesters" as asserted by the Examiner. Without waiving this deficiency, the foregoing amendments canceling claims 12-20 obviate this rejection.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

3. Rejection of Claims 1-11 under 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 1-11 under 35 U.S.C. § 112, first paragraph, for the following reasons:

> "The instant specification invites the skilled artisan to experiment. The factors which must be considered in determining undue experimentation are set forth in In re Wands 8 USPQ2d 1400. The factors include:

1) quantity of experimentation necessary,
2) the amount of guidance presented,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the predictability of the art,
7) breath of the claims and in the
8) level of skill in the art.

Quantity of experimentation necessary, Amount of guidance presented, Presence or absence of working examples

Claims 1-11 are drawn to a method for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal, comprising administering to said animal an effective amount of a urea or carbamate of heterocyclic ester or amide.

There is not seen adequate representation in the instant specification to support the claims cited supra with regard to treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal.

An inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In the case of the instant specification, there is not seen adequate representation wherein the compound of the invention are administered to diverse *in vivo* systems, i.e. human, birds, fish, reptiles, etc. and memory is enhanced or treatment of impairment is

demonstrated in those with or without the various disorders correlated with sufficient data or guidance to memory and vision functions *in vivo*.

Applicant cites mice treated with GP 1046 and subjected to the Morris water maze used for assessing spatial memory formation and retention in experimental animals as an example of support for the claim to treating memory impairment or enhancing memory performance in an animal. Applicants sole animal model utilized mice and the improvements to memory were confined to that of spatial memory. However, there is not seen adequate representation wherein dosages for diverse animal species was given and disorders such as Alzheimer's, amnesia, Korsakoff's syndrome, etc. have been treated with the compounds of the invention and an improvement in the disorder was demonstrated.

Given that the visual systems vary between animal species as well as the multitude of vision disorders arising from various etiologies, a claim to the treatment of vision disorder or improving vision should be supported with adequate representation commensurate to the breadth and scope of the claim(s). The examples cited by applicant to support the claims cited supra are not treatments, but rather suppositions that if the compounds of the invention are administered to various visual disorders such as uveitis, conjunctivitis, chronic exposure to ultraviolet light an improvement is expected. This is not seen as sufficient guidance or adequate representation(s) to support the treatment claims cited supra. Without the benefit of protocols for a diversity of animal systems such as dosages, routes of administration, one of skill in the art would be subject to undue experimentation in the practice of the invention.

State of the Art

The state of the art is such that no singular compound or class of compounds is known to exhibit activity for improving the broad spectrum of visual disorders and memory impairments. Wherein compounds such as phosphatidyl serine and choline have shown slight improvements in aiding short term memory and applicant's

background of the field of this invention details various compounds which are effective for specific neurotrophic or vision disorders, but the art has not recognized the use of one agent which will broadly provide improvement in healthy states as well as impaired states for the host of visual disorders and memory impairments as instantly asserted. Where the art fails to provide guidance for making and using a singular class of compounds to support a broad spectrum of therapeutic efficacy, the specification submitted to provide enablement for such should necessarily provide such support to substantiate same.

Breadth of the claims

The instant claims are drawn to a method for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal, comprising administering to said animal an effective amount of an N-linked sulfonamide of a heterocyclic thioester compound. As drafted, the claimed compounds of the invention would seem to encompass treatment for a broad range of disorders for both vision and memory such as refractive disorders such as myopia and hyperopia; astigmatism; glaucoma; blindness- color or night; eye socket disorders such as orbital cellulitis, Cavernous Sinus Thrombosis, exophtalmos; and disorders of the Conjunctiva; eyelid and tear gland disorders such as blepharitis; Corneal Disorders such as Superficial Punctate Keratitis, Corneal Ulcer, Keratomalacia; Cataracts, Retinal Disorders such as Macular Degeneration, Retinal Detachment, Retinitis Pigmentosa, Arteriosclerotic Retinopathy, Hypertensive Retinopathy, Retinal Artery Blockage, Retinal Vein Blockage and Diabetic Retinopathy; Optic Nerve Disorders such as Papilledema, Papillitis, Retrobulbar Neuritis and Toxic Amblyopia; Alzheimer's; Amnesia; Korsakoff's syndrome. One of skill in the art would recognize that there is no singular compound or class of compounds which would provide treatment or improvement for the broad spectrum of disorders cited supra. Moreover, applicants singular example is not seen to be to demonstrative of art recognized test systems which would provide a correlation for the improvement of the broad spectrum of disorders cited supra."

Contrary to the Office Action, the present application does not claim an "N-linked sulfonamide of a heterocyclic thioester compound" as asserted by the Examiner. Without waiving this deficiency, Applicants respectfully traverse this rejection on the basis that a *prima facie* case of nonenablement has not been established. By law, a patent application is presumptively enabled when filed. "As a matter of Patent Office practice...a specification...must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). As pointed out by the PTO in the *35 U.S.C. § 112 First Paragraph Enablement Training Manual* (citing In re Wright, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a [nonenablement] rejection." Applicants respectfully submit that a *prima facie* case of nonenablement has not been established because the Office Action fails to advance any such "reasoned or supported statements".

Even if a *prima facie* case has been established, it would be rebuttable for the reasons set forth below.

The Examiner contends that Applicants' working examples are insufficient to enable the full scope of the disorders sought to be treated by the claimed methods. In particular, the Examiner asserts without any supporting evidence that the "the state of the art is such that no singular compound or class of compounds is known to exhibit activity for improving the broad spectrum of visual disorders and memory impairments." Even assuming that the assertion is true despite the lack of supporting evidence, the absence of viable treatments has not deterred the USPTO from granting numerous patents claiming methods of improving vision and enhancing memory. Contrary to the Examiner's argument, the U.S. patents show that the art does "provide guidance for making and using a singular class of compounds to support a broad spectrum of therapeutic efficacy."

The Examiner further asserts that the application lacks adequate details of experimental protocol, and that the results of the Morris Water Maze and Optic Nerve Transection and Regeneration (ONTR) tests do not support memory enhancement or vision improvement. A specification need not describe that which is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Not only is the protocol for the Morris Water Maze test well known in the art, countless U.S. patents rely upon Morris Water Maze experimental data to support

claims for treating memory impairment. See, for example, U.S. Patents Nos. 5,852,029 and 5,739,119, copies attached. Further, McNamara, et al., "The neuropharmacological and neurochemical basis of place learning in the Morris water maze", *Brain Res. Reviews*, 18:33-49 (1993), copy attached, disclose the Morris Water Maze test as a recognized animal model for learning and memory. The protocol for ONTR is equally well known[1], and ONTR experimental data have similarly been relied upon in numerous U.S. patents to support claimed methods of improving vision. See, for example, U.S. Patent No. 5,800,812, copy enclosed.

The Examiner further asserts that there is insufficient correlation between Applicants' experimental data and the "diverse

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[1]See, e.g., Dewaza, et al., *Role of Swann Cells in Retinal Ganglion Cell Axon Regeneration*, Prog. Retin. Eye Res., 19(2):171-204 (2000); Watanabe, et al., *Environmental Light Enhances Survival and Axonal Regeneration of Axotmized Retinal Ganglion Cells in Adult Cats*, Exp. Neurol., 160:133-141 (1999); Quan, et al., *Survival of Axotomized Retinal Ganglion Cells in Peripheral Nerve-grafted Ferrets*, Invest. Ophthalmol. Vis. Sci., 40(10):2360-2366 (1999); Dewaza, et al., *Glial Cells in Degenerating and Regenerating Optic Nerve of the Adult Rat*, Brain Res. Bull., 48(6):573-579 (1999); Cui, et al., *CNTF, Not Other Trophic Factors, Promotes Axonal Regeneration of Axotomized Retinal Ganglion Cells in Adult Hamsters*, Invest. Ophthalmol. Vis. Sci., 40(3):760-766 (1999); Oh, et al., *Functional Properties of Retinal Ganglion Cells During Optic Nerve Regeneration in the Goldfish*, Vis. Neurosci., 15(6):1145-1155 (1998); Lazarov-Spiegler, et al., *Peripheral Nerve-stimulated Macrophage Simulate a Peripheral Nerve-like Regenerative Response in Rat Transected Optic Nerve*, Glia, 24(3):329-337 (1998); and Fukuda, et al., *Functional Recovery of Vision in Regenerated Optic Nerve Fibers*, Vision Res., 38(10):1545-1553 (1998).

in vivo systems" to which the claimed methods are administered. Contrary to the Examiner's position, courts have long accepted laboratory animal data as enabling for methods of treating humans and other *in vivo* systems. See, for example, *In re Jolles*, 206 USPQ 885, 890 (CCPA 1980)(court held that experimental tests with laboratory mice enabled methods for treating leukemia in humans). Based on Applicants' disclosure in combination with that which is well known in the art, one of ordinary skill in the art can extrapolate from the working examples to the likely operability of all physiological embodiments encompassed by the claims.

Finally, the Examiner concludes that "one of skill in the art would be subject to undue experimentation in the practice of the invention." Controlling authority holds that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). As discussed above, the Morris Water Maze and ONTR tests are well described in the application and well known in the art. Thus, regardless of the cost or time entailed by the tests, the testing protocols are merely routine to one of ordinary skill in the art.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

4. Rejection of Claims 1-6 under 35 U.S.C. § 112, second paragraph

The Office Action rejects claims 1-6 under 35 U.S.C. § 112, second paragraph, for the following reasons:

> "Claim 1 is seen as vague and indefinite as applicant cites a method for improving vision, however applicant has not established a baseline or specific measure (be it unit of measure or otherwise) of what constitutes vision improvement. For instance, it is unclear as to whether applicant is improving color recognition, depth perception, or alleviating conditions such as myopia, astigmatism, etc. and to what degree of alleviation or improvement is intended. Also, claim 1 is vague and indefinite in the recitation of a heterocyclic ester without setting forth a definitive structure. Given the broad number of compounds which are encompassed by heterocyclic esters applicant should particularly point out and distinctly claim what structure or compound is intended. Accordingly, dependent claims 2-6 are rejected as they fail to obviate the rejections set forth in the parent claim.

Applicants respectfully traverse the rejection of claims 1-6. Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, for example, *In re Marosi*, 710 F.2d 799, 218 U.S.P.Q.

289 (Fed. Cir. 1983); *Rosemont, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984).

"Improve" is ordinarily defined as "to make greater in ... degree; augment; to enhance in ... degree" (Websters *Third International Dictionary*, Merriam-Webster Corp., New York, 1971). As defined in the present application, "'Vision' refers to the ability of humans and other animals to process images...." Thus, "improving vision" refers to an increase, augmentation, or enhancement of the ability to process images. The increase, augmentation, or enhancement is necessarily relative to a previously-existing state. Since vision improvement for any patient will vary depending upon the patient's vision prior to treatment, a generalized baseline or specific measurement for vision improvement cannot be established. It is clear from the specification that "improving vision" includes improving color recognition, depth perception, visual impairment or any other known measure of vision.

Further, "improving vision" is well-known language conventionally used in the art to which the claimed invention pertains. The USPTO has granted numerous patents claiming methods of improving vision. Many of these patents, such as U.S. Patent No. 5,955,102, copy attached, do not even define "vision", let alone establish a baseline or specific measure of vision

improvement.

"Heterocyclic ester" is similarly a well-known term understood by persons of ordinary skill in the art to represent a heterocyclic ring substituted with an ester. In addition, the application exemplifies "heterocyclic ester" with numerous generic structures and species. See Formulas I-IV and Tables I, II and VIII.

A broad claim, no matter how broad, is not indefinite as long as the boundaries of the claim are capable of being understood. *In re Gardner*, 427 F.2d 786, 166 U.S.P.Q. 138 (C.C.P.A. 1970). Thus, regardless of the number of compounds or the breadth of conditions encompassed by the terms "heterocyclic ester" and "improving vision", the claims satisfy the second paragraph of 35 U.S.C. § 112 because when read in light of the specification or that which is known in the art, they reasonably apprise to those skilled in the art the metes and bounds of the claimed subject matter.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

5. Rejection of Claims 12-20 under 35 U.S.C. § 102(e) or 35 U.S.C. § 103(a)

The Office Action rejects claims 12-20 under 35 U.S.C. § 102(e) as being anticipated by or, in the alternate, as obvious over U.S. Patent No. 5,786,378. As the basis for this rejection,

the Office Action states:

> "Claims 12-20 are drawn to a pharmaceutical composition for treating a vision disorder, improving vision, treating memory impairment or enhancing memory performance in an animal, comprising administering to said animal an effective amount of a heterocyclic ester and a pharmaceutically acceptable carrier.
>
> The pharmaceutical compositions of heterocyclic esters of Formula I of the instant claims have been set forth as pharmaceutical compositions in the claims and disclosure of '378. Hamilton et al. also teach aromatic substitutions such as unsubstituted or substituted mono, bi- or tricyclic, carbo- or heterocyclic rings with the compounds of the invention (col.3- col.9). The claims of the instant application differ only by the addition of further alkyl and aromatic groups, which constitute obvious substitutions in the Markush groups of the analogous compounds set forth in '378.
>
> As the '378 patent teaches substitution of aromatic groups with the heterocyclic esters, it would have been obvious to one of skill in the art that further aromatic groups such as substituted (in 1-3 positions) furanyls, etc. could also serve as aromatic substituents."

The foregoing amendments canceling claims 12-20 obviate this rejection.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is believed to be enabled and to be patentably distinguishable over the art of record. The Examiner is

therefore respectfully requested to reconsider and withdraw the rejections of claims 1-20 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcome to telephone the undersigned attorney with those questions or comments.

Respectfully submitted,

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